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(54) Title: PHARMACEUTICAL VEHICLES FOR REDUCING TRANSDERMAL FLUX

(57) Abstract

Method of inducing a reservoir effect in skin and mucous membranes so as to enhance penetration and retention and reduce transdermal flux of topically applied therapeutic and cosmetic pharmacologically active agents. The invention also relates to topical treatment methods involving such reservoir effect enhancers, and to pharmaceutical compositions containing them.

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PHARMACEUTICAL VEHICLES FOR REDUCING TRANSDERMAL FLUX

Field of the Invention

Method of inducing reservoir effect in skin and mucous membranes so as to increase penetration and residence time of pharmacologically active agents therein.

Background of the Invention

There are many localized disease conditions which are effectively treated by topical application of suitable physiological agents. In order for such treatments to be maximally effective, it is necessary that as much of the pharmacologically active agent as possible be absorbed into the skin where it can make contact with the disease condition in the dermal tissues without being lost by rubbing off on clothing or evaporation. At the same time, the agent must not penetrate so effectively through the skin as to be rapidly lost to the lymphatic and vascular circulatory systems. This latter factor is especially important when the pharmacologically active agent is toxic when used systemically.

The ideal vehicle for topically applied pharmaceuticals is therefore one which can produce a "reservoir effect" in the skin of mucous membranes to which the topical

treatment is applied. This "reservoir effect" is defined as an enhancement of the skin or membrane's ability to both absorb and retain pharmacologically active agents, i.e., to increase skin or membrane residence time, decrease drug transit time and reduce transdermal flux.

A number of compounds are known to enhance the ability of pharmacologically active agents to penetrate the skin and mucous membranes, for example, N-bis-azacyclopentan-2-onyl-alkanes, 1-substituted azacyloheptan-2-ones and higher alkyl-substituted azacyclopentan-2-ones, as well as dimethylsulfoxide and lower alkyl sulfoxides. These compounds, however, have the disadvantage of allowing rapid systemic dispersion of the pharmacologically active agents away from the localized site of pathology. Many topical medicaments, such as the retinoids used in the treatment of acne, and methotrexate, used in the treatment of psoriasis, are systemically toxic. The retinoids, for example,are known to cause damage to unborn fetuses. Thus, there is a need for a method of enhancing the ability of such medicaments to penetrate into the skin or mucous membrane so that a lesser total dosage may be used, while at the same time retarding their ability to move from the skin to the interior of the body.

The problem posed by the paradoxical requirement that a systemically toxic topical medicament be efficiently absorbed into, but not through the skin, has heretofore gone unrecognized. There have been no vehicle additives available to the pharmacological industry which act to enhance the "reservoir capacity" of the skin and mucous membranes so that the amount of pharmacological active agents reaching and being retained at the site of localized pathologies is maximized.

Summary of the Invention

This invention is a method for inducing a reservoir effect in skin and mucous membranes so as to enhance penetration and retention of topically applied pharmacologically active therapetuic and cosmetic agents therein. The invention also relates to topical treatment methods involving such reservoir effect enhancers, and to pharmaceutical compositions containing them.

The additives of this invention are water-soluble zinc-containing compounds, preferably zinc halide, zinc sulfate, zinc nitrate, zinc acetate, and/or zinc stearate, and most preferably zinc chloride.

The pharmacologically active agents with which the water-soluble zinc-containing compounds are used are preferably those containing hydroxyl, oxo, sulfhydryl, amine, carboxyl, and other anionic groups in configurations which readily allow complexation or chelation with zinc ions.

In inducing a reservoir effect in the skin and mucous membranes to reduce transdermal flux so that drugs are abosrbed and retained therein in larger amounts for longer periods of time than has heretofore been possible, the water-soluble zinc-containing compounds of this invention act as potentiators for the pharmacologically active agents. Potentiation is defined as overcoming or reducing undesirable effects such as systemic toxicity and extending the range of effectiveness of the pharmacologically active agent, or both.

DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph of test results showing the skin reservoir effect achieved by the method of this invention utilizing nordihydroguaiaretic acid with zinc chloride, as compared to the same compound without zinc chloride. The nordihydroguaiaretic acid was labelled with carbon-14 for radiotracer analysis. The graph shows immediate absorption and longer retention of larger amounts of the nordihydroguaiaretic acid with zinc chloride present than without. The availability of nordihydroguaiaretic acid, a lipoxygenase inhibitor, to therapeutically act upon localized pathologies, both with and without added zinc chloride, is measured by the areas under the respective curves. It is apparent that skin bioavailability is greatly enhanced in the presence of a zinc-containing compound. The drug flux rate can be calculated as a function of the area under the curve by dividing this area by dose. As is apparent, drug flux rate is substantially decreased over the entire dosage range by the addition of zinc chloride.

DETAILED DESCRIPTION OF THE INVENTION

The zinc-containing compounds of this invention are generally any water-soluble organic or inorganic zinc salts which dissociate in the topical vehicle so as to provide zinc ions which may complex or chelate with the pharmacologically active agents present in the vehicle. Examples of suitable zinc-containing compounds are zinc halide, zinc sulfate, zinc nitrate, zinc acetate, and/or zinc stearate. The most preferred zinc-containing compound is zinc chloride.

Such water-soluble zinc-containing compounds may be prepared by means known to the art, and many are commercially available.

The topical preparations of this invention having enhanced reservoir inducing capacities may be prepared by mixing, by means known to the art, a water-soluble zinc-containing compound into the pharmaceutical preparation or vehicle in which a reservoir-inducing capacity is to be created so as to promote the presence of zinc ions in the mixture which may complex or chelate with the pharmacologically active agents. It is believed that such a complexation or chelation is not necessary to obtaining the benefits of the invention provided zinc ions are present in a mixture containing the pharmacologically active agent. In any event, the presence of other metallic ions which would unfavorably compete with zinc for complexation or chelation sites is to be avoided. The zinc salt can also be mixed with the pharmacologically active agent which is then incorporated into the pharmaceutical carrier.

The mechanism by which the reservoir-inducing effect of this invention is produced is not known; however, it is preferred that the pharmacologically agents contain hydroxy, oxo, sulfhydryl, amine, carboxyl, or other anionic groups, or combination thereof in conformations which allow complexation and/or chelation by zinc ions.

The zinc-containing compounds are preferably present in an equimolar ratio with the pharmacologically active agents, so as to cause maximum enhancement of reservoir inducing capacities. Where stratum corneum destruction, i.e., decornification, is desirable, an excess of such zinc-containing compounds which also act as escharotics, e.g., zinc chloride, may be used. (Generally, concentrations of 35% (0.257 moles per 100 grams) or more zinc chloride will cause tissue destruction when topically applied.) Normally, use of equimolar concentrations of zinc chloride and the pharmacologically active agent will not involve the use

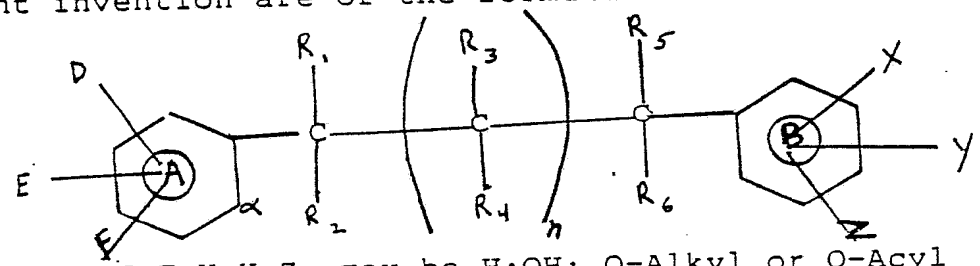
of escharotic amounts of zinc chloride, however, less than 35% zinc chloride should be considered an upper limit when no escharotic effect is desired. Less than an equimolar ratio of zinc-containing compound to pharmacologically active agent may be employed where it is not desired that all the medicament be absorbed into the skin or mucous membranes, e.g., in connection with mouthwash and douche preparations where attack on free-swimming organisms is also desirable.

Other ingredients may be added to the preparations, including coloring agents, stability-enhancing agents, antioxidants, and the like. Preferably these additives will not compete with the pharmacologically active agents for zinc; however, when necessary, excess zinc-containing compounds may be used to compensate for the zinc complexing or chelating effecting of such additives.

The pharmacologically active agents of this invention are those intended for topical application to achieve localized therapeutic or cosmetic effects. A partial list of suitable pharmacologically active agents includes steroids, antifungals, anti-unicellular microorganism agents, antiviral agents, antiparasitic agents, antineoplastic agents, anti-leprosy agents, antimetabolites, cell-regulatory agents, immuno - pharmacological agents, allergens, antihistaminic agents, anti-inflammatory agents, anesthetic agents, analgesic agents, anti-seborrheic agents, analgesics, anti-pretic agents, anti-asthma agents, anti-gout agents, anti-convulsant agents, anti-hypertensive agents, anti-diabetic agents, anti-migraine agents, anti-ychotic agents, anti-Parkinson agents, anti-allergy agents, anti-spasmodic agents, anti-tussive agents, anti-asthmatic agents, anti-anginal agents, hypolipidemic agents, contraceptives, scabicides, anti-

wart agents, enzyme inhibitors, fertility agents, vasodilators, H_2 receptor antagonists, anti-ulcer agents, muscle relaxants, counter-irritants, vitamins, nutrients, diagnostic agents, radiopaque agents, cryoprotective agents, perfumes, insect repellants, hair dyes, anti-carring agents, sun screens, melanin-stimulating agents, antiperspirants, antisecretory agents, depilatories, hair restorers, wrinkle-reducing agents, antidandruff agents, emollients, rubifacients, and cosmetic agents in general.

The catecholic butanes useful in the compositions of the instant invention are of the formula



wherein, D,E,F,X,Y,Z, may be H;OH; O-Alkyl or O-Acyl optionally substituted with hydroxy, alkoxy, substituted amino, carboxyl, or carbalkoxy;

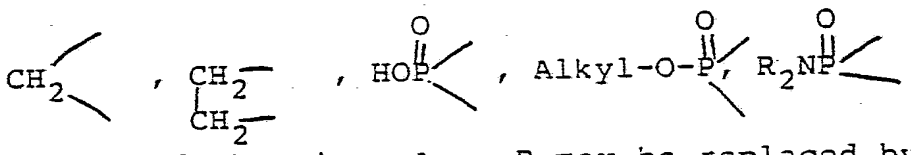
R_1-R_6 may be H; lower alkyl or lower alkoxyl optionally substituted with hydroxy, alkoxy, substituted amino, carboxyl, or carbalkoxyl; hydroxy; carbonyl; alkoxy; aryl; aralkyl;

n may be 0 to 5;

any of the aromatic rings in the molecule may contain up to 3 substituents from the following list: hydroxy; alkenoxy; alkyl, alkoxy or alkanoyl optionally substituted by hydroxy, alkoxy, substituted amino, carboxy, or carbalkoxy; CF_3; halo; carboxy; carbalkoxy; cyano; hydroxymethyl; sulfonic acid; sulfonamido; aminosulfonyl (i.e. - $NHSO_2R$); nitro; alkoxy-carbonyloxy; aminocarbonyloxy; aroyloxy; aralkanoyloxy;

heteroaroyloxy; glycosidyloxy; and

any two phenolic groups may be joined together by the following groups:



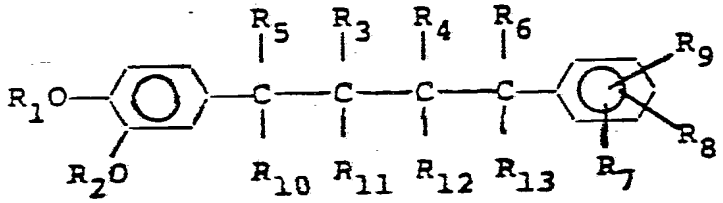
either of the rings A or B may be replaced by cyclohexyl, napthyl, tetrahydronapthyl, pyridyl, piperidinyl, quinolinyl, indanyl, indenyl;

any of the groups R_1 to R_6 may be joined together to form together with the other carbons to which they are attached, a5, 6, or 7 membered ring optionally interrupted by an oxygen atom, or containing an oxygen atom and a carbonyl substituent, or containing a carbonyl substituent;

any of the groups R_3 to R_6 may be joined to ring A to form with it a 5, 6, or 7 membered ring;

any of the carbons in the chain between rings A and B, may be attached by a bond to the α position on ring A to form a 5, 6, or 7 membered ring.

The preferred catecholic butanes useful in the compositions of the instant invention are of the Formula



(II)

wherein R_1 and R_2 are independently H, lower alkyl or lower acyl;

R_3, R_4, R_5 and R_6 are independently H or lower alkyl;
R_7, R_8 and R_9 are independently H, hydroxy, lower alkoxy

or lower acyloxy;

R_{10}, R_{11}, R_{12}, and R_{13} are independently H or lower alkyl.

Lower alkyl is intended to generally mean C_1-C_6 alkyl, and preferably R_3 and R_4 are C_1- C_3 alkyl. Lower acyl is intended to generally mean [C_1-C_6] acyl, with [C_2-C_6] being preferred. It will be appreciated by those skilled in this are that Formula II is directed to both the phenolic compounds and the conventional esters and ethers thereof.

Illustrative classes of compounds within the scope of Formula (II) are those wherein:

a) one or more of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{12}, and R_{13} are H, e.g., those wherein R_5 is H, R_5 and R_6 are H or R_5, R_6 and R_7 are H and R_8 and R_9 are OH or OR_1;

b) R_3 and R_4 each are CH_3 or C_2H_5 including those of a), especially those wherein R_5, R_6, and R_7 are H and/or R_8 and R_9 are OH and OR_1;

c) R_1 and R_2 are lower acyl, e.g., hydrocarbonacyl, preferably, alkanoyl, e.g., acetyl, propionyl, etc., including those of a) and b);

d) R_1 and R_2 are alike and R_8 and R_9 are OR_1 including those of a), b) and c); and

e) The compound is in the form of a single optical isomer or a mixture of such isomers, e.g., a racemic mixture or diastereoisomers including each of a), b), c) and d).

As used herein, lower alkyl represents, inter alia, methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, and the like.

Lower acyl represents groups having the general formula RCO-, e.g., acetyl (CH_3CO-), propionyl (CH_3CH_2CO-), butyryl ($CH_3CH_2CH_2CO-$), and the like. When the catecholic butane compound is named as a substituted phenyl, the corresponding groups are acetoxy (CH_3CO_2-), propionyloxy ($CH_3CH_2CO_2-$), and butyroyloxy ($CH_3CH_2CH_2CO_2-$).

Other preferred pharmacologically active agents of this invention include:

1. Antineoplastic agents including NDGA (nordihydroguaiaretic acid), VP-16 (epipodophyllotoxin beta-D ethylidene glucopyranoside--etoposide), VM-26 (epipodophyllotoxin beta-D thenylidene glucopyranoside--teniposide), 4' dimethyl epipodophyllotoxin, diethylstibestrol, dithranol, cyclophosphamide, mitomycin, daunomycin, plantinum cis-diamine - dichloride, adriamycin, allopurinol, 5-fluorouracil, and methotrexate.

2. Immunopharmacological agents which may be topically applied including polypeptide nanoparticles comprising interleuken or active fragments thereof, antibodies or active-fragments thereof, interferons, and liposomes. Such delivery systems providing sustained release of pharmacologically active agents are effectively localized or held in place by zinc according to this invention.

3. Steroids, which are utilized for a wide range of therapeutic purposes including anti-inflammation, antipruritic, enhancement of moisture retention, etc.,

including: dexamethasone, hydrocortisone, hydrocortisone acetate, hydroxy hydrocortisone, hydrocortisone valerate, triamcinolone acetonide, triamcinolone hexacetonide, amoinonide, fluocinolone acetonide, fluocinonide, flurandrenolide, difluorasone diacetate, betamethasone dipropionate, betamethasone, betamethasone benzoate, betamethasone valerate, halcinoide, desoximethasone, desonide, prednisolone, and clocortolone pivalate.

4. Antifungal agents which are used to treat fungus infections on the skin, hair, and nails, such as athlete's foot (tinea pedis), jock itch (tinea cruris), and ringworm (tinea corporis), which can be caused by a number of fungi, particularly Tricophyten rubrum, Trichophyten mentagrophytes, Epidermophyton floccosum, and Microsporum canis. These antifungal agents include haloprogin, iodochloro, miconazole nitrate, tolnaftate, thiabendazole, chloroxine, amphotericin, candicin, fungimycin, nystatin, chlordantoin, clotrimazole, ethonam nitrate, miconazole itrate, pyrrolnitrin, fezatione, ticlatone, tolnaftate, triacetin, carbonic acid derivatives; dithiocarbamate, thiourea, thiocynates; aromatic carboxylic acids and the amides thereof, benzoic acid, salicylic acid, salicylic acid amide and anilide; aromatic sulfides, polysulfides, and sulfoxides, 5,5-dichloro-2,2 dihydroxydiphenylsulfide; invert soaps, quaternary ammonia and phosphonium compounds, decamethylene-bis-(4-thio-pyridine-methyl - tosylate; quinoline derivatives, 8-hydroxyquinoline sulfate, halogenated quinolines, 7-iodo-8-hydroxy-quinoline-5-sulfonic acid, 5-chloro-7-iodo-8-hydroxy-quinoline, 5-chloro-8-hydroxy-quinoline, 5,7-dichloro-8-hydroxyquinaldine, 5,7-diiodo-8-hydroxy-quinoline, decamethylene-bis (4-amino-quinaldium chloride); benzothiazole derivates, (2-dimethylamino-6-(beta-diamino-ethoxy)-benzothiazole dihydrochloride; imidazole

derivatives, 1-(0-chloro-alpha-alpha -diphenyl-benzyl)-imidazole, 1-[o,p-dichloro-beta-(o,p - dichlorobenzyloxy)-phenethylimidazole]; benzimidazole derivatives, 2-phenylbenzimidazole, 2-furfurylbenzimidazole; thiadizine derivatives, 3,5-dibenzyltetrahydro-1,3,5-thiadizine-2-thinoe; furan derivatives, 5-nitro-2-furfuryl-3-chloropropionate; quinones, tetrachloro-p-benzoquinone, 1,4-naphthoquinone, phenanthraquinone; sulfonamides and sulfones; aromatic diamidines, 2-hydroxystilbamidine, and diamidinodiphenyl-amine.

Antifungal agents are also used to treat vaginal infections caused by Candida albicans and related yeasts; these agents include dioctyl sodium sulfosuccinate, haloprogin, miconazole nitrate, potassium sorbate, propionate compounds, such as calcium propionate and sodium propionate, sodium lauryl sulfate, clotrimazole, tolnuftate, griseofulvin, ketronazole, moconazole and nystatin.

5. Antibacterial agents, which are utilized for treating skin infections such as impetigo, ecthymus, folliculitis, boils, and acute pronychia, and for treating skin wounds and as a wound cleanser, and which may be used in this invention, including sulfonomides, penicillins, cephalosporins, penicillinase, lincomycins, vancomycins, tetracylines, chloramphenicols, and streptomycins; including within this group the following compounds: gramicidin, neomycin, polymyxin beta sulfate, tetracycline, benzethonium chloride, gentamicin sulfate, nitrofurazone, benzalkonium chloride, hexylresorcinol, chloroxylenol, cloflucarban, carbolic acid (phenol), triclocarban, and triclosan.

6. Antiviral agents, including those used to treat warts, such as glacial acetic acid, ascorbic acid,

calcium pantothenate, lactic acid, salicylic acid, cantharidin, and podophyllin, and antiviral agents used to treat cold sores or herpes simplex such as acyclovir, benzalkonium chloride, alcohol, allantoin, anhydrous glycerin, benzocaine, camphor, carbamide peroxide, lanolin, menthol, petrolatum, and phenol; and antiviral agents including those used to treat herpes genitalis such as urea, idoxuridine, amantadine, methisazone, cytarabine, interferons, chloroform, ether, bacillus calmette-guerin and levamisole.

7. Antiparasitic agents including antihelmintic agents (agents that destroy or expel intestinal worms) capable of penetrating the skin of the animal to be treated, e.g., benzimidazole compounds, tetramisole, levamisole, and isoquinoline compounds, diloxanide, metronidazole, suramin, quinine, primethamine, primaquine PO_4, benzyl benzoate.

8. Pediculicides, for mites (or scabies) and lice, including lidane, pyrethrins, piperonyl butoxide, malathion, and crotamiton.

9. Acne treatment compounds including benzoyl peroxide, resorcinol, resorcinol monoacetate, sulfur, povidone-iodine, salicylic acid, phenol, fluocinolone acetonide, para-aminobenzoic acid, sodium thiosulfate, meclocyline sulfosalicylate, sodium sulfacetamide, tetracycline hydrocholoride, aliphatic dicarboxylic acids, e.g., adipic and azelaic acids, and sulfurated lime.

10. Antipsoriasis agents inclusing cytostatic agents, which retard skin-cell growth, keratolytic agents, which loosen and dissolve scales, tar preparations, whose mode of action is uncertain; hydrocortisone preparations, which reduce itching and inflammation; anti-itch preparations, and antimicrobials. These antipsoriasis

agents include coal tar preparations, juniper tar, pine tar, allantoin, saponated cresol, menthol, mercury oleate, phenol preparations, resorcinol, salicylic acid, anthralin, and methotrexate.

11. Leprosy agents including 4-4'-diaminodiphenyl sulfone.

12. Anesthetic agents for pain and itching, inflamed skin, sunburn, insect bites, wounds, hemorrhoids, poison ivy, and poison oak, including: benzocaine, lidocaine, lidocaine hydrochloride, dibucaine, dibucaine hydrochloride, procaine, tetracaine, tetracaine hydrochloride, pramoxine hydrochloride, benzyl alcohol, diperodon, butamben picrate, cyclomethycaine sulfate, and dimethisoquin hydrochloride.

13. Analgesic agents for pain and itching, inflamed skin, sunburn, insect bites, burns, wounds, hemorrhoids, poison ivy, poison oak, including: salicylic acid derivatives; N,N-dimethyl aspartic acids; N-N-dimethyl glutamic acid, trolamine salicylate, methyl salicylate; antipyrine, aspirin, and salicylamide.

14. Counter-irritants (agents applied locally to produce an inflammatory reaction with the object of distracting and relieving a deep seated inflammatory process) including methyl salicylate, camphor, menthol, eugenol, eucalyptol, thymol, allyl isothiocyanate (mustard oil), capsicum preparations, histamine dihydrochloride, methyl nicotinate, and turpentine oil.

15. Antihistamines which are used principally against itching but are also midly anesthetic, including diphenhydramine hydrochloride, phenyltoloxamine dihydrogen citrate, pyrilamine maleate, tripelennamine hydrochloride.

16. Diagnostic agents including allergenic extracts for diagnosis and immunotherapy of specific allergy offenders from the following categories: pollens, foods, dusts, epidermals, insects and stinging insects, fungi, molds, yeasts, tests for sensitivity to therapeutic pencillin (benzyl-penicilloyl-polylsine); tests for sensitivity to tetanus antigens, diphtheria antigens, streptococcus antigens, tuberculin, Candida antigens, Trichophyton antigens, and Proteus antigens.

17. Vitamins and nutrients for skin, hair, and scalp conditions including anti-scarring agents, vitamins B_3, B_5, B_6, A, D, and E.

18. Cosmetic agents and perfumes including compositions to reduce the appearances of wrinkles such as water soluble elastin and pregnenolone; skin depigmenting agents and bleaches, including hydroquinone and monobenzone.

19. Sunscreens including: dioxybenzone, oxybenzone, padimate 0, padimate A, aminobenzoic acid, cinoxate, diethanolamine p-methoxycinnamate, ethyl 4-[bis(hydroxypropyl)] aminobenzoate, ethylhexyl salicylate, glyceryl aminobenzoate, homosalate, the combination of lawsone and dihydroxyacetone, red petrolatum, and sulisobenzone.

20. Antimetabolites including methoprexate, 5 fluorouraul, cytosine arabinoside, 5-azacytidine, and mercaptopurine.

21. Immunomodulators including cyclosporin A, cyclophosphamide, chlomabucil, azathioprine, BCG, levamisole, thymosin.

22. Hair restorers including minuxidil, hydralazine,

sodium nitroprusside, captopril.

The foregoing are simply examples of pharmacologically active agents including therapeutic and cosmetic agents which may be used with enhanced effectiveness for their known properties in accordance with this invention.

In addition to the reservoir effect produced by zinc ions in skin and mucous membranes, a direct potentiating effect has been observed when pharmaceutical preparations containing zinc ions and pharmacologically active agents are injected directly into diseased tissues, particularly solid tumors. The mechanism for this potentiating effect is not known; however, it may be caused by a reservoir-inducing effect directly on the tissues involved.

Dosage forms for topical application may include lotions, ointments, creams, gels, suppositories, nasal solutions, mouthwashes, sprays, aerosols and the like. Typical carriers which make up the foregoing dosage forms include water, acetone, isopropyl alcohol, stearyl alcohol, freons, ethyl alcohol, polyvinyl pyrrolidone, propylene glycol, polyethylene glycol, fragrances, gel-producing materials, mineral oil, stearic acid, spermaceti, sorbitan, monoleate, polysorbates, "Tweens," sorbitol, methyl cellulose, etc. Typical formulations of the pharmaceutical compositions of this invention are set forth in Table I below:

Application	Formulation	(Per 100 Mgs.)
Anti-Inflammatory (Steroid) Ointment	PEG 400	10
	PEG 8000	60
	Zinc acetate	0.8
	Valerate	0.05
	Parabens	0.05
	Water	23.95
	Stearyl alcohol	5
		100.00
Antiparasitic	Benzyl Alcohol	0.5

Application	Formulation	(Per 100 Mgs.)
(Vaginal Trichomonocide) Cream	Ascorbyl Palmitate	0.2
	Propylene glycol	10.00
	Metronidazole	0.25
	Zinc gluconate	0.1
	Water	35.4
	Stearyl alcohol	7.5
	Cetyl Alcohol	4.5
	White Petrolatum	34
	Mirj 52	7
		100.00
External Antifungal Lotion	Ascorbic Acid	0.1
	Polyoxyethylene sorbitan	5
	Sorbitan monopalmitate	5
	Mineral Oil	15
	Petrolatum	15
	Spermacetti	5
	Water	53.4
	Tolnaftate	1
	Zinc chloride	0.5
		100.00
Psoriasis gel containing methotrexate (antimetabolite)	Ascorbic acid	0.1
	SDA 40-2	10.0
	Propylene glycol	22.0
	Water	43.4
	Laureth 4	6.0
	Xantham gum	3.0
	Zinc acetate	1.0
	Methotrexate	0.25
	Parabens	0.05
		100.00
Psoriasis occlusive ointment containing azathioprine (immunomodulation)	Sorbitan sesquioleate	3.5
	Sorbitan monolaurate	1.5
	Stearyl Alcohol	15.0
	Azathioprine	0.01
	Zinc Gluconate	0.1
	Polyvinyl alcohol	15
	Propylene glycol	7.5
	Water	53.89
		100.00
Insect Repellent Lotion	N,N-diethyl-N-toluamide (DEET)	23.4
	Zinc sulfate	1.5
	Alcohol	74.6
	Paraben	0.05
		100.0
Sunscreen	PABA	5

Application	Formulation	(Per 100 Mgs.)
	PEG-12	5
	Glycerin	2
	Triathanolamine	0.175
	Carbomer 940	0.4
	Water	87.425
		100.000
Vitamin E Gel	Vitamin E	20.0 IU
	Zinc glutonate	0.05
	Water	92.425
	Glycerin	2
	Carbowax 600 (PEG 12)	5
	Carbopol (Carbomer 940)	0.4
	Na_2C0_3 (in 10 ml. H_20)	0.025
		100.000
Hair Restorer Gel	Minoxidil	5
	Zinc acetate	1
	BHA	0.1
	Propylene glycol	10
	Alcohol (SDA 95%)	10
	Poloxomer F 127	25
	Water, Purified	46
	Capryl Alcohol (C8)	2.9
		100.00
Antibacterial Water Washable Cream	Stearyl Alcohol	15
	Beeswax	8
	Sorbitan monooleate	1.25
	Polysorbate 80 USP	3.75
	Gentamicin	0.2
	Zinc acetate	0.5
	Sorbitol solution USP	7.5
	Water	63.55
	Ascorbic palmitate	0.2
	Parabens	0.05
		100.00

The amount of the composition, and thus of the pharmacologically active agent therein to be administered, will obviously be an effective amount for the desired result expected therefrom. This, of course, will be ascertained by the practitioner utilizing his ordinary skill. Due to enhanced activity which is achieved, the dosage of agent may often be decreased from that generally applicable. In accordance with usual prudent formulating practices, a dosage near the

lower useful range of the particular agent may be employed initially and the dosage increased as indicated from the observed response.

The following examples are included by way of illustration and/or by way of limitation. Unless otherwise indicated, the nordihydroguaiaretic acid used in the instant examples was the meso-isomer and is designated NDGA. Other isomers are indicated, e.g., d, l-NDGA.

EXAMPLE 1

Antineoplastic Preparation

Two compositions utilizing zinc chloride, nordihydroguaiaretic acid (NDGA), acid (EDTA), butylated hydroxytolulene (BHT), stearyl alcohol, purified water, polyethylene glycol having an average molecular weight of 400 (PEGO 400), and polyethylene glycol having an average molecular wight of 3350 (PEGO 3350) were prepared in the following manner: the purified water was placed in a clean glass container of suitable capacity; the water was heated to about 80-90°C with stirring; and zinc chloride was added to the heated water, continuing the stirring until the zinc chloride dissolved. The ethylenediaminetetraacetic acid was slowly added with mixing until dissolved. In a separate glass container of suitable size, the polyethylene glycol 400 was heated to about 80-90°C with stirring; the NDGA was added thereto; then the BHT; and this mixture was added to the zinc chlorideethylenediaminetetraacetic acid solution with stirring. The entire mixture was then cooled to about room temperature and passed through a number 3 roller mill until smooth. The polyethylene glycol 3350 was then heated to about 80-90°C in a suitable container and

the milled ingredients added thereto with mixing.

The final compositions in wt/wt % were as follows:

TABLE 1

	Compound	
Composition	A	B
zinc chloride	29.8	10.0
NDGA	4.6	4.6
EDTA	14.7	4.93
BHT	1.1	1.1
stearyl alcohol	0.5	0.5
H20	18.3	18.3
PEGO 400	26.4	26.4
PEGO 3350	4.5	4.5

EXAMPLE 2

Reservoir Effect

This study was designed to provide basic pharmacokinetic data on the disposition of Carbon 14 (^{14}C) labelled nordihydroguaiaretic acid (NDGA) applied dermally in modified compounds A and B described in Example 1. In addition, the distribution of zinc was measured for the dermally applied Compound A.

The ^{14}C-NDGA compound exhibited a specific radioactivity of 20.2 Ci/mole (66.9 micro Ci/mg) and a purity of 96.9% by mass spectrometry and by radioautography of thin-layer chromatography plates developed in benzene:isopropanol:acetic acid:water (25:5:2:10).

Subsequently, 25.1 mg of the ^{14}C-NDGA-Compound (66.9 micro Ci/mg) were mixed with 12.35 g of Compound A. Analyses of triplicate samples of the final mixture for

^{14}C by counting and for NDGA by high-pressure liquid chromatography (HPLC) demonstrated homogeneity, with a content of 51 micro g of ^{14}C-NDGA compound/mg of Compound A. The specific radioactivity of the NDGA was 3.00×10^3 micro Ci/micro g.

Similarly, 26.3 mg of the original ^{14}C-NDGA compound (66.9 micro Ci/mg) were mixed with 12.55 of Compound A devoid of Zn and EDTA to obtain a mixture for the study of the dermal penetration of NDGA from Compound A devoid of Zn and EDTA. Analysis of triplicate samples of the modified Compound A showed the final mixture to be homogeneous with regard to ^{14}C and NDGA; it contained 53 micro g of ^{14}C-NDGA compound/mg of vehicle. The specific radioactivity of the diluted NDGA was 3.41 x 10-3 micro Ci/micro g.

The compounds were dermally applied to young adult Sprague-Dawley rats by the following protocol: under ether anesthesia, the back skin of the rat was prepared by removing the hair from a 5 x 5-cm area with a clipper and the residual hair stubble was removed with a wax depilatory. Then the skin was stripped repeatedly (5X) with adhesive tape until the stratum corneum was removed. Then 0.5 gm of the formulation was weighted on a 5 x5-cm sheet of polypropylene, which was applied to the prepared skin. It was secured in place by hypoallergenic tape.

Finally, the bandage was overwrapped with bandage tape. After treatment, the rats were caged individually in metabolism cages, which allowed free access to food and water and provided for separate collection of urine and feces.

The testing of Compound A with ^{14}C-NDGA was performed in 15 male Sprague-Dawley rats (means weight 339 $\pm$ 16 g).

They received an average of 0.520 (± 0.032) g of Compound A containing 14C-NDGA. The mean dose of ^{14}C-NDGA was 78.5 (± 7.0) mg/kg of body weight. The rats were housed invdividually in metabolism cages providing for free access to food and water and for the separate collection of urine and feces. Groups of 3 rats were sacrificed at 4, 24, 48, 72 and 96 hr and excreta were collected from each rat during 24-hr periods. In addition to the usual collection of tissues, the skin site of application was excised after wiping the site with water-moistened tissue. The wipes were added to the wrappings, which were immersed in a small container of acetone.

The testing of Compound A devoid of Zn and EDTA was performed on 15 male Sprague-Dawley rats (mean weight 241 ± 7 g). They received an average of 0.390 (± 0.019) g of Zn-free Compound A containing ^{14}C-NDGA. The average dose of ^{14}C-NDGA was 83.2 mg/kg of body weight. Groups of three rats were bled terminally and tissues were taken at 4, 24, 48, 72, and 96 hr after dosing. As each sacrifice time, those three rats scheduled to be sacrificed next were also bled nonterminally from the orbital sinus. The wrappings and wipes of the skin site were taken at the time of sacrifice and added to acetone as described above.

The results of the study are given in Table 2A for Compound A containing ^{14}C-NDGA and Table 2B for Zn-Free Compound A containing ^{14}C-NDGA. The results of analysis for tissue distribution of zinc as a percent of dose in rats receiving Compound A containing ^{14}C-NDGA are given in Table 2C.

TABLE 2A

Tissue Distribution of ^{14}C as a Percent of Dose in Rats Receiving Compound A containing ^{14}C-NDGA, Dermally

Tissue	Mean (+ S.D.)[a] Percent of the Dose of ^{14}C Found at Hours				
	4	24	48	72	96
Organs (%)	4.62 (± 2.27)	7.55 (± 1.85)	10.29 (±8.8)	10.43 (±6.94)	13.45 (±3.45)
Skinsite (%)	20.8 (±8.4)	19.6 (±5.2)	11.1 (±1.4)	8.58 (±5.41)	7.01 (±2.28)

$a_N = 3$

TABLE 2B

Tissue Distribution of ^{14}C as a Percent of Dose in Rats Receiving Zn-Free Compound A Containing (±8.4)-NDGA, Dermally

Tissue	Mean (+ S.D.)[a] Percent of the Dose of ^{14}C Found at Hours				
	4	24	48	72	96
Organs (%)	10.28 (±6.12)	11.08 (±9.65)	10.47 (±10.33)	5.41 (±4.21)	8.03 (±1.48)
Skinsite (%)	4.15 (±0.76)	12.20 (±5.9)	7.86 (±3.75)	4.72 (±3.18)	1.43 (±0.55)

$a_N = 3$

TABLE 2C

Tissue Distribution of Zn as a Percent of Dose in Rats Receiving Compound A, Dermally

Tissue	Mean Percent of the Dose of Zn Found at Hours				
	4	24	48	72	96
Organs (%)	3.28	6.54	6.79	11.47	12.69
Skinsite (%)	10.5	11.8	9.58	6.46	4.99

$a_N = 3$

The study was continued for testing Compound B with 14C-NDGA; Zn- and EDTA-free Compound B; and modified Compound B with no BHT and 0.10 EDTA. The following Table 2D lists the compositions of the compounds and the amounts of materials used for preparing the compounds containing ^{14}C-NDGA. These compounds were analyzed for ^{14}C by scintillation counting and for NDGA by liquid chromatography.

TABLE 2D

	Composition (%)		
Constituents	Compound B Formulation	Zn-Free Compound B Formulation	Modified Compound B Formulation
Compound Zn	10.00	0.00	10.00
Compound EDTA	4.93	0.00	0.10
Compound NDGA	4.60	4.60	4.60
Compound BHT	1.10	1.10	0.00
Water, purified	18.32	18.32	19.42
PEG 400	2.60	14.50	14.19
PEG 8000	53.45	49.39	46.69
Stearyl Alcohol	5.00	12.09	5.00
	100.00	100.00	100.00
Compounds containing ^{14}C-NDGA:			
mg of ^{14}C-NDGA	25.75	25.40	25.20
g. of Formulation	12.55	12.55	12.75
% NDGA in final mixture	4.80	4.79	4.78

The mean rat body weights, average doses of the formulations, and mean doses of ^{14}C-NDGA in mg/kg of body weight for the three current protocols were: 297±15 g (standard deviation), 512 ± 28 mg, and 82.7 ± 2.0 mg/kg for Compound B; 325 ± 12 g, 570 ± 26 mg, and 84.0 ± 1.4 mg/kg for Zn-Free Compound B; and 328 ± 27 g, 575 ± 45 mg, and 84.2 ± 2.8 mg/kg for modified Compound

B. Fifteen rats were used for each study and groups of three rats were sacrificed at 4, 24, 48, 72 and 96 hr after dosing. At each time, blood, liver, skin site, intestines and contents, carcass, and combined wrappings and wipes were collected. Also, from the groups sacrificed at 24, 48, 72 and 96 hr urine, feces, and cage washings were collected.

The results of the study are given in Table 2E for Compound B; Tabel 2F for Zn-free Compound B; and Table 2G for modified Compound B.

TABLE 2E

Tissue Distribution of ^{14}C-NDGA as a Percent of Dose in Rats Receiving Compound B Containing ^{14}C-NDGA, Dermally

Tissue	Mean (± S.D.)[a] Percent of the Dose of ^{14}C Found at Hours				
	4	24	48	72	96
Organs (%)	1.92 (±1.34)	4.41 (±1.44)	4.31 (±2.5)	3.38 (±0.52)	1.87 (±1.1)
Skinsite (%)	16.3 (±9.2)	11.8 (±6.1)	8.92 (±4.10)	6.55 (±1.76)	5.11 (±3.01)

[a] $a_N = 3$

TABLE 2F

Tissue Distribution of ^{14}C as a Percent of Dose in Rats Receiving Zn-free Compound B Containing ^{14}C-NDGA, Dermally

Tissue	Mean (± S.D.)[a] Percent of the Dose of ^{14}C Found at Hours				
	4	24	48	72	96
Organs (%)	1.16 (±0.92)	2.29 (±2.26)	2.38 (±1.73)	7.39 (±10.05)	7.73 (±10.9)
Skinsite (%)	2.21 (±1.44)	4.45 (±4.36)	6.07 (±2.90)	18.6 (±6.3)	12.0 (±4.99)

$a_N = 3$

TABLE 2G

Tissue Distribution of ^{14}C as a Percent of Dose in Rats Receiving Modified Compound B Containing ^{14}C-NDGA, Dermally

Tissue	Mean (± S.D.)[a] Percent of the Dose of ^{14}C Found at Hours				
	4	24	48	72	96
Organs (%)	4.35 (±3.06)	1.65 (±0.68)	4.41 (±3.57)	2.54 (±2.05)	0.96 (±0.19)
Skinsite (%)	14.4 (±7.1)	23.0 (±5.5)	17.1 (±4.7)	16.3 (±0.6)	17.7 (±6.2)

aN = 3

The above results show that the addition of the water-soluble zinc-containing compound causes the organic molecule to more quickly absorb into the skin in larger quantities, and to be retained in the skin longer than when the zinc-containing compound is not present.

EXAMPLE 3

Antineoplastic Enhancement

For the organic compounds listed, in the case of those having two or more benzene rings, .0145 moles per 100 cc's was used, and for those having one or no benzene rings, .029 moles per 100 cc's was used. The organic compound was measured into a clean vial and PEGO 400 was added with mixing until dissolved.

For the test compounds containing zinc chloride, zinc chloride was first dissolved in the PEGO 400 to prepare a stock solution containing 0.69% zinc chloride, and this solution was added with mixing to the vials containing the organic compounds being tested.

These compounds were tested with and without zinc chloride for their effectiveness as antitumor agents against xenografts of human breast adenocarcinoma, MX-1, grown in athymic (nude) mice of Balb/c background by intratumor injection according to the following protocol: each animal was innoculated intradermally on the dorsum near the nape of the neck with 0.05 ml of an MX-1 tumor homogenate. Tumor weights, in milligrams, were calculated from a measurement of the length, width and height in millimeters of the tumors using the formula (L x W x H)/2. The animals were randomized in groups to ensure representation of smaller and larger tumors. The tumors were treated by intratumor injection with 0.10 ml of each test composition. Each composition was tested utilizing five animals. The animals were treated only once. Results are set forth in Table 3.

TABLE 3

Organic Compound Known Anti-Cancer Agent	Tumor Free 60 Days	Premature Death	Tumor at Death	Tumor Re-currence
VP-16 (no Zn)	2	2	3	0
VP-16 + Zn	5	0	0	0
*1/5 VP-16 + Zn	3	0	2	2
VM-26 (no Zn)	0	0	5	0
VM-26 + Zn	5	0	0	0
*1/5 Vm-26 + Zn	5	0	0	0
4'-demethylepipo-dophyllotoxin (no Zn)	1	0	4	3
4'-dimethylepipo-dophyllotoxin + Zn	5	0	0	0
diethylstilbestrol (no Zn)	0	2	5	0
diethylstilbestrol + Zn	3	0	2	1
dithranol (no Zn)	1	0	4	0
dithranol + Zn	4	0	1	1
cyclophosphamide (no Zn)	0	0	5	0
cyclophosphamide + Zn	3	2	0	0
mitoymcin (no Zn)	1	4	2	0
mitomycin + Zn	5	0	0	0
daunomycin (no Zn)	3	2	5	3
daunomycin + Zn	5	0	0	0
platinum cis-diamine -dichloride (no Zn)	1	0	4	0
platinum cis-diamine -dichloride + Zn	5	0	0	0
adriamycin (no Zn)	0	1	2	4
*1/10 adriamycin (no Zn)	2	1	2	2
adriamycin + Zn	4	0	1	1
*1/10 adriamycin + Zn	1	3	1	1

TABLE 3 (Continued)

Organic Compound Known Anti-Cancer Agent	Tumor Free 60 Days	Premature Death	Tumor at Death	Tumor Re-currence
allopurinol (no Zn)**	0	--	5	—
*5/2 allopurinol (noZn)	0	0	5	0
*5/2 allopurinol + Zn	1	0	4	4

* Dosage level decreased or increased or indicated.

** All sacrified on day 25.

These results show the reduced toxicity and enhanced antineoplastic effectiveness achieved by the addition of zinc ions.

EXAMPLE 4

Antineoplastic Potentiation

Compositions and organic compounds not previously known as antineoplastic agents were prepared with and without zinc chloride according to the procedure of Example 3 and tested for their ability to eradicate turmors following the protocol described in Example 3. Results are set forth in Table 4.

TABLE 4

Organic Compound	Tumor Free 60 Days	Premature Death	Tumor at Death	Tumor Recur-currence
3-tertbutylphenol (no Zn)	1	3	1	0
3-tertbutylphenol + Zn	5	0	0	0
4-tertbutylphenol (no Zn)	5	0	0	0

TABLE 4 (Continued)

Organic Compound	Tumor Free 60 Days	Premature Death	Tumor at Death	Tumor Recurrence
4-tertbutylphenol + Zn	5	0	0	0
p-hydroxycinnamic acid (no zinc)	1	0	4	0
p-hydroxycinnamic acid + Zn	4	1	0	0
norisoguaiacin (no Zn)	2	1	1	0
norisoguaiacin + Zn	5	0	0	0
dl-NDGA (no Zn)	4	0	1	0
dl-NDGA + Zn	5	0	0	0
azelaic acid (no Zn)	1	0	4	0
azelaic acid + Zn	5	0	0	0
1-(3,4-diacetoxyphenyl -4-phenylbuta-1,3-diene (no Zn)	1	0	4	0
1-(3,4-diacetoxyphenyl) -4-phenyl-buta-1,3-diene + Zn	3	0	2	2
1,4-bis(3,4 -dihydroxphenethyl) -benzene (no Zn)	2	0	3	3
1,4-bis(3,4 -dihydroxyphenethyl) -benzene + Zn	2	0	3	3

These results show that the antineoplastic activity of drugs can be increased to worthwhile levels while at the same time reducing toxicity utilizing zinc ions.

EXAMPLES 5-10

Enhancement of Topical Antineoplastic Agents

In Examples 5-10, wherein reference is made to the

testing of mixtures for antitumor activity against B-16 melanoma and Sarcoma-180 solid tumor growth in mice, the following procedures were utilized. To the extent that a particular example modified the procedure, such modification will be indicated in the particular example.

Both types of tumors were grown intradermally or subcutaneously in the mice. The B-16 melanoma was grown in BDF1 mice and the S-180 tumor was grown in ICR mice. Each mouse was injected intrademally with about 0.01 ml of a saline suspension containing about 1 x 10^6 cells of the tumor cells per 0.01 ml into a preshaven area on the back of the neck of the mouse. The tumors were allowed to grow until they had an approximate size of about 25-100 mg, calculated by the length of the tumor multiplied by the width and height of the tumor measured in millimeters and dividing the product by two. On the first day of treatment, the animals with tumor sizes outside of the size range were culled and the remaining animals were randomly divided into control and test groups. When the tumors had reached the appropriate size, usually at about day six, the tumors were punctured uniformly and then treated with either a test compound or a control by topical application to the surface of the tumor. Generally, two topical applications were made 24 hours apart. The materials were applied to obtain from about a 1 to about 2 mm coating over the surface of the tumor. The animals were thereafter observed and their weights and the size of their tumors were periodically measured.

The results of each of the experiments include the following:

(a) the starting number (n) of animals within a treatment group of an experiment;

(b) the average tumor size in milligrams of the animals treated with the mixture and the average tumor size of the control animals;

(c) the ratio multiplied by 100 of the average size of the tumors of the treated animals to that of the control animals (T/C), wherein T = average size of treated mice and C = average tumor size of control mice;

(d) the percentage of both treated and control animals clear of tumor; and

(e) the percentage of animals of the original number surviving.

The later three measurement for a particular experiment were all taken at the same time and range generally from 21 to about 33 days after tumor innoculation. A T/C value of 42 or less is indicative of activity. In all of the following tables for Examples 5-10, the control results are given in parenthesis ().

EXAMPLE 5

Two formulations of meso-NDGA were prepared in a PEGO base. Their compositions are set forth in Table 5.

TABLE 5

Mixture	NDGA (meso)	H20	EtOH	PEGO 3350
1	3.6	24.3	48.5	23.4
2	6.9	0	0	93.1

Mixture No. 1 was prepared by dissolving the NDGA in absolute ethanol by warming and stirring; thereafter the water was added slowly to the NDGA solution. The

mixture was heated to evaporate sufficient solvent to obtain a mixture of about 130% of the weight of the NDGA, and was then incorporated into the PEGO base. Mixture No. 2 was made by simply dissolving the NDGA in the PEGO base with warming and stirring.

EXAMPLE 6

The NDGA formulations of Example 5 were tested for potential antitumor activity against B-16 melanoma grown in mice. The procedure utilized was that previously described. The results are given below in Table 6.

TABLE 6

n	T/C[1]	Tumor Size (Control)	% Clear (Control)	% Survival (Control)
9	87	954±698 (1091±547)	0 (0)	33 (80)
9	114	748±621 (645±335)	0 (0)	77 (77)
10*	24	138±99 575±270	20 (0)	100 (60)

EXAMPLE 7

Several formulations of zinc chloride in a PEGO base were prepared by first dissolving the zinc chloride in water and then mixing the zinc chloride solution into the PEGO base. The formulations had approximately the following weight/weight percent compositions as set forth in Table 7.

TABLE 7

Mixture	ZnCl2	H20	PEGO
3	41.9	11.6	46.5
4	30	16	53.8
5	14.6	4.1	81.3
6	28.6	7.9	63.5
7	46.1	13.8	40
8	15	8	77
9	13.8	9.2	77
10	5.5	3.7	90.8

EXAMPLE 8

Mixtures of Example 7 were tested for potential antitumor activity against B-16 melanoma and S-180 solid tumor grown in mice in accordance with the procedures previously described. The results are given in Table 8.

TABLE 8

S-180

Mixture	n	T/C[1]	Tumor Size (Control)	% Clear (Control)	% Survival (Control)
3	8	51	559±476	25	100
			(1095±360)	(10)	(100)
3	10	40	366±345	11	90
			(934±656)	(10)	(100)
6	8	48	524±462	12	100
			(1095±360)	(10)	(100)
6	10	115	1074±687	10	100
			(934±656)	(10)	(100)
7	5	0	0	100	80
			(752±511)	(0)	(100)
7	10	0	0	100	90
			(550±184)	(0)	(100)
7	10	0	0	100	100

TABLE 8 (Continued)

S-180

Mixture	n	T/C[1]	Tumor Size (Control)	% Clear (Control)	% Survival (Control)
			(997±421)	(0)	-
10	8	74	815±421)	0	87
			(1095±360)	(10)	(100)
3	10	6	162±253	60	100
			(2505±1844)	(0)	(100)
4	10	16	106+114	30	100
			(644±342)	(0)	(70)
5	10	47	1119±764	22	90
			(2505±1844)	(0)	(100)
6	10	4	94±217	80	100
			(2505±1844)	(0)	(100)
7	9	15	169±216	37	88
			(1091±547)	(0)	(80)
7	9	0	0	100	88
			(654±335	(0)	(77)
7	10	2	31±100	90	100
			(1805±968)	(0)	(80)
8	10	43	277±209	10	40
			(644±342)	(0)	(70)
9	10	1.0	25+63	80	90
			(1732±2254)	(70)	(80)

EXAMPLE 9

Mixtures of zinc chloride, EDTA and NDGA were prepared and formulated in a PEGO base. The mixtures were prepared by dissolving the NDGA and EDTA in a portion of the PEGO base by warming and stirring until dissolved. The zinc chloride was dissolved in water and warmed. The zinc chloride solution was added to the warm PEGO containing the NDGA and EDTA and stirred until cooled to room temperature. The composition of the mixtures is

given in approximate weight/weight percentage as set forth in Table 9.

TABLE 9

Mixture	ZnCl2	NDGA	EDTA	H20	PEGO
11	27.5	6.9	14.7	18.3	32.6
12	28	6.81	14.7	18.2	32.9

EXAMPLE 10

The mixtures of Example 9 were tested for thier potential antitumor activities against B-16 melanomas grown in mice in accordance with the procedure previously described. The results are given in Table 10.

TABLE 10

Mixture	n	T/C[1]	Tumor Size (Control)	% Clear (Control)	% Survival (Control)
11	10	8	51±118	70	100
			(711±286)	(0)	(100)
12	10	0	0	60	100
			(711±286)	(0)	(100)

1 - T/C ratio calculated at day 24 except for Mixture 11 which was calculated at day 21.

The foregoing Examples 5-10 show the potentiating effect of zinc chloride on antineoplastic agents topically applied, showing improvement over the antineoplastic activity of zinc chloride alone, and comparable amounts of NDGA even when the NDGA is injected into the tumor.

EXAMPLE 11

Appropriate human and animal modes are chosen for the disease conditions treated by the following compounds as hereinabove described, and the compounds tested to determine effective and toxic dosages with and without the addition of equimolar amounts of zinc chlordie, zinc iodide, zinc bromide, zinc sulfate, zinc nitrate, zinc stearate, and zinc acetate. From the results the Therapeutic Index, equivalent to ratio of toxic to effective dosage is calculated, and this Index for the compounds with and without zinc additives compared to show an increase in Therapeutic Index for compounds containing zinc additives as compared to compounds without such additives: NDGA (nordihydroguaiaretic acid), VP-16 (epipodophyllotoxin beta-D ethylidene glucopyranoside --etoposide), VM-26 (epipodophyllotoxin beta-D thenylidene glucopyranoside--teniposide), 4'dimethyl epipodophyllotoxin, diethylstilbestrol, dithranol, cyclophosphamide, mitomycin, daunomycin, platinum cis-diamine-dichloride, adriamycin, allopurinol, 5-fluroouracil, methotrexate, dexamethasone, hydrocortisone, hydrocortisone acetate, hydroxyl hydrocortisone, hydrocortisone valerate, triamcinolone acetonide, triamcinolone hexacetonide, amcinonide, fluocinolone acetonide, fluocinonide, flurandrenolide, difluorasone diacetate, betamethasone dipropionate, betamethasone, betamethasone benzoate, betamethasone valerate, halcinonide, desoximethasone, desonide, prednisolone, clocortolone pivalate, haloprogin, iodochloro, miconazole nitrate, tolnaftate, thiabendazole, chloroxine, amphotericin, candicin, fungimycin, nystatin, chlordantoin, clotrimazole, ethonam nitrate, miconazole nitrate, pyrrolnitrin, fezatione, ticlatone, tolnaftate, triacetin, dithiocarbamate, thiourea, thiocyantes; aromatic carboxylic acids and the amides thereof, benzoic acid, salicylic acid, salicylic acid amide and anilide; aromatic sulfides, polysulfides, and sulfoxides, 5,5-

dichloro-2, 2-dihydroxydiphenylsulfide; quaternary ammonia and phosphonium compounds, decamethylene-bis-(4-thio -pyridine-methyl-tosylate; 8-hydroxyquinoline sulfate, halogenated quinolines, 7-iodo-8-hydroxy-quinoline-5 -sulfonic acid, 5-chloro-7-iodo-8-hydroxy-quinoline, 5-chloro-8-hydroxy-quinoline, 5,7-dichloro-8-hydroxy -quinaldine, 5,7-diiodo-8-hydroxyquinoline, decamethylenebis (4-amino-quinaldium chloride); (2-dimethylamino-6-(beta-diaminoethoxy)-benzothiazole dihydrochloride; 1-(0-chloro-alpha-alpha-diphenyl-benzyl) -imidazole, 1-[0,p-dichloro-beta-(0,p-dichlorobenzyloxy) -phenethylimidazole]; 2-phenylbenzimidazole, 2-furfurylbenzimidazole; 3,5-dibenzyltetrahydro-1,3,5 -thiadizine-2-thione; 5-nitro-2-furfuryl-3-chloropropionate; quiones, tetrachloro-p-benzoquinone, 1,4-naphthoquinone, phenanthraquinone; sulfonamide sulfones, aromatic diamidines, 2-hydroxy-stilbamidine, diamidinodiphenylamine, dioctyl sodium sulfosuccinate, miconazole nitrate, potassium sorbate, calcium propionate and sodium propionate, sodium lauryl sulfate, penicillin, cephalosporin, penicillinase, lincomycins, vancomycin, tetracylkne, chloroamphenicol, sterptomycin, gramicidin, neomycin, polymxxin beta sulfate, tetracycline, benzethonium chloride, gentamicin sulfate, nitrofurazone, benzalkonium chloride, hexylresorcinol, cholorxylenol, diloroflurcarban, carbolic acid (phenol), triclocarban, triclosan, glacial acetic acid, ascorbic acid, calcium pantothenate, lactic acid, salicyclic acid, cantharidin, podophyllin, acyclovir, benzalkonium chloride, alcohol, allatoin, anhydrous glycerin, benzocaine, camphor, carbamide peroxide, lanolin, menthol, petrolatum, phenol, idoxuridine, amantadine, methisazone, cytarabine, interferon, chloroform, ether, bacillus calmette-guerin, levamisole, benzimidazole, tetramisole, levamisole, isoquinoline lidane, pyrethrin, piperonyl butoxide, malathion, crotamiton, benzoyl peroxide, resorcinol

monoacetate, sulfur, povidone-iodine, phenol, fluocinolone acetonide, para-amino -benzoic acid, sodium thiosulfate, meclocyline sulfosalicylate, sodium sulfacetamide, tetracycline hydrochloride, 6-2 carbonaliphatic dicarboxylic acids, sulfurated lime coal tar, juniper tar, pine tar, allantoin, saponated oresol, menthol, mercury oleate, phenol, methotrexate 4-4'-diaminodiphenyl sulfone, benzocaine, lidocaine, lidocaine hydrochloride, dibucaine, dicubaine hydrochloride, procaine, tetracaine, tetracaine hydrochloride, tronothane, dyolonine, dyclonine hydrochloride, pramoxine hydrochloride, benzyl alcohol, diperodon, butaben piorate, cyclomethycaine sulfate, dimethisoquin hydrochloride, N,N-dimethyl aspartic acid; N-N-dimethyl glutamic acid, trolamine salicylate, methyl salicylate; antipyrine, salicylamide, camphor, euguenol, eucalyptol, thymol, allyl isothiocyanate (mustard oil), capsicum preparations, histamine dihydrochloride, methyl nicotinate, turpentine oil, diphenhydramine hydrochloride, phenyltoloxamine dihydrogen citrate, pyrilamine maleate, tripelennamine hydrochloride, tetanus antigen, diphtheria antigen, streptococcus antigen, tuberculin, Candida antigen, Trichophyton, Proteus antigen, vitamins B3, B5, B6, A, D, and E, elastin, pregenolone, hydroquinone, monobenzone, dioxybenzone, oxybenzone, padimate 0, padimate A, aminobenzoic acid, cinoxate, diethanolamine p-methoxycinnamate, ethyl 4-[bis(hydroxypropyl)] aminobenzoate ethylhexyl salicylate, glyceryl aminobenzoate, homosalates, lawsone, dihydroxyacetone, red petrolatum, and sulisobenzone.

The foregoing examples are illustrative of the methods and compositions of this invention and are not intended to be limiting. The present invention is believed to be a pioneering invention in the area of drug potentiation, and as such embraces many equivalents not specifically

described herein.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition that enhances skin and mucous membrane retention ability comprising a pharmacologically active agent having a reactive group selected from the group consisting of hydroxyl, oxo, sulfhydryl, amine, carboxyl and ionic zinc.

2. The composition according to claim 1 wherein the pharmacologically active agent is a complex or chelate of zinc.

3. A method of enhancing the skin and mucous membrane retention of a pharmacologically active agent selected from the gorup consisting of VP-16 (epipodophyllotoxin beta-D ethylidene glucopyranoside--etoposide); VM-26 (epipodophyl-lotxin beta-D thenylidene glucopyranoside -- teniposide); 4'-demethyl epipodophyllotoxin; diethylstilbestrol; dithranol; cyclophosphamide; mitomycin; daunomycin; platinum cis-diamine-dichloride; adriamycin; and allopurinol; said method comprising adding to said agent an effective amount of water-soluble zinc -containing compound.

4. The method of Claim 1 wherein said zinc-containing compound is zinc chloride.

5. A pharmaceutical composition that enhances skin and mucous membrane retention ability comprising a pharmacologically active agent selected from the gorup consisting of VP-16 (epipodophyllotoxin beta-D ethylidene glucopyranoside --etoposide); VM-26 (epipophyllotoxin beta-D thenylidene glucopyranoside--tneiposide); 4'1 demethyl epipodophyllotoxin; diethylstilbestrol; dithranol;

cyclophosphamide; mitomycin; daunomycin; platinum cis-diamine-dichloride; adriamycin; and allopurinol; and an effective amount of a water-soluble zinc-containing compound.

6. The composition of Claim 3 wherein said zinc-containing compound is zinc chloride.

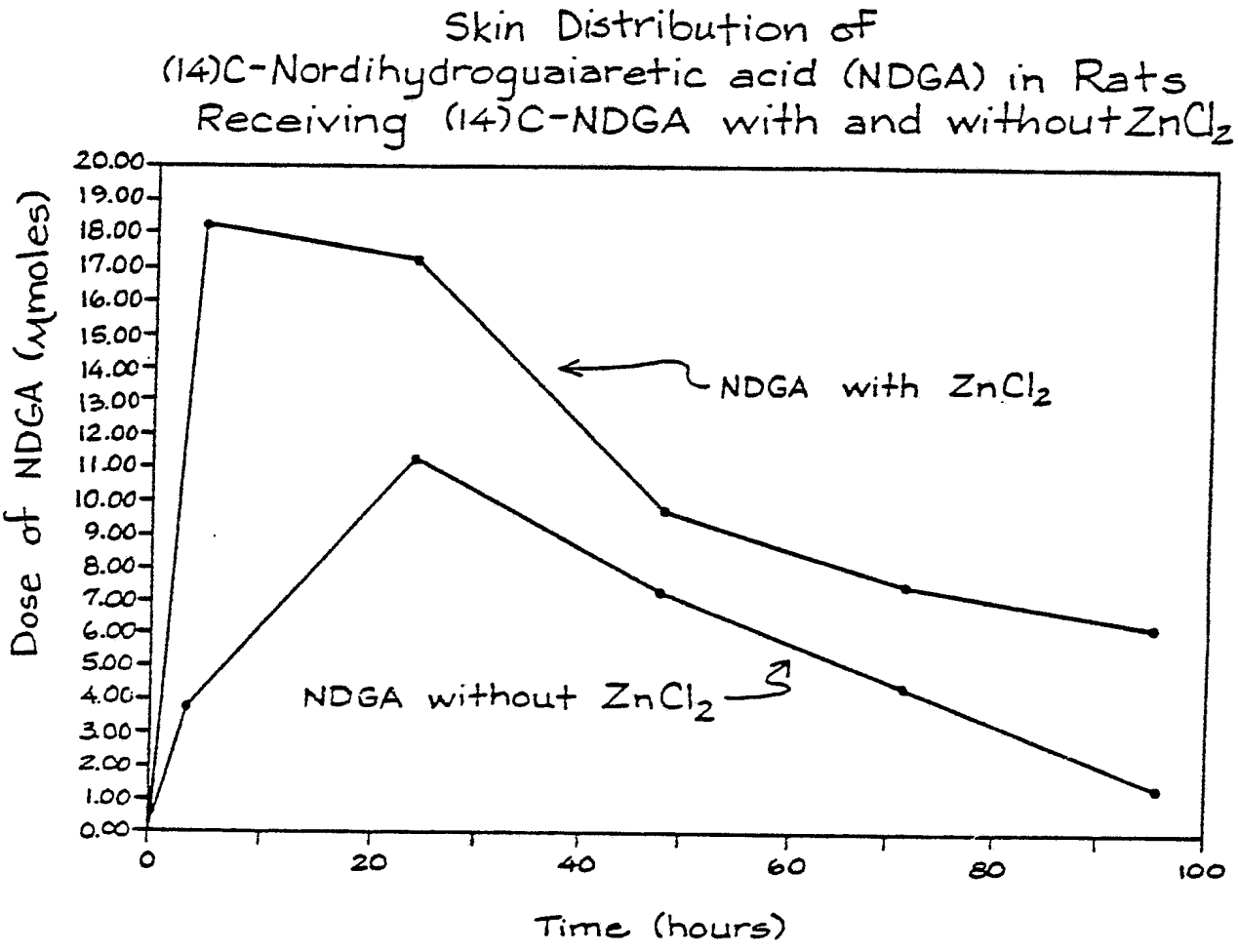


FIGURE 1

INTERNATIONAL SEARCH REPORT

International Application No PCT/US86/02544

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

INT. CL.[4] A61K 31/05, 31/28, 31/40, 31/66, 31/71, 31/505
U.S. CL: 514/33,34,110,258,410,492,732,733; 424/145

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	514/33,34,110,258,410,492,732,733 424/145

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	US,A, 3,660,578 (HATA ET AL) Published 02 May 1972, see Col. 2, lines 1-35.	1-6
Y	US,A, 4,039,663 (ARCAMONE ET AL) Published 02 August 1977, see Col. 1, lines 7-8.	1-6
Y	US,A, 4,203,969 (YARROW ET AL) Published 20 May 1980, See Col. 1, lines 7-9.	1-6
Y	US,A, 4,406,881 (LADANYI) Published 27 September 1983, See Col. 1, lines 10-16 and 66-68.	1-6

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
05 February 1987	10 FEB 1987
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	Elli Peselev

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No [18]
Y	US,A, 4,469,684 (HUGGINS ET AL) Published 04 September 1984, See Col. 14, lines 41-50.	1-6
X	US,A, 4,537,883 (ALEXANDER ET AL) Published 27 August 1985, See Col. 1, lines 10-16.	1-6
Y	US,A, 4,564,675 (KURABAYASHI ET AL) Published 14 January 1986, See Col. 1, lines 67-68 and Col. 2, line 45.	1-6
Y	US,A, 4,567,253 (DURST ET AL) Published 28 January 1986, See Col. 1, lines 60-61.	1-6